Case Report

Depot Pure GnRH Antagonist for Long-term Treatment of Ovarian Hyperthecosis Monitored by Multisteroid LCMS Profiling

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Abbreviations: $17OHP_4$, 17 hydroxyprogesterone; $17OHP_5$, 17 hydroxypregnenolone; A_4, androstenedione; DHEA, dehydroepiandrosterone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LCMS, liquid chromatography mass spectrometry; LH, luteinizing hormone; OHT, ovarian hyperthecosis; T, testosterone.

Abstract

Ovarian hyperthecosis (OHT), severe hyperandrogenism after menopause in the absence of ovarian or adrenal tumors, is usually treated by surgical excision. We report a 58-year-old woman presenting with severe hyperandrogenism (serum testosterone 15.7-31.0 nmol/L, normal female <1.8 nmol/L) with menopausal gonadotropins and virilization but no adrenal or ovarian lesions. Multisteroid profiling by liquid chromatography mass spectrometry (LCMS) of adrenal and ovarian vein samples identified strong gradients in the left ovarian vein (10- to 30-fold vs peripheral blood in $17OHP_4$, 17 hydroxyprogesterone, 17 hydroxypregnenolone, androstenedione, testosterone, dehydroepiandrosterone) but the right ovarian vein could not be cannulated with the same findings in a second ovarian vein cannulation. OHT diagnosis was confirmed by an injection of a depot pure gonadotropin-releasing hormone (GnRH) antagonist (80 mg Degarelix, Ferring) producing a rapid (<24 hour) and complete suppression of ovarian steroidogenesis as well as serum luteinizing hormone and follicle-stimulating hormone lasting at least 8 weeks, with reduction in virilization but injection site reaction and flushing and vaginal spotting ameliorated by an estradiol patch. Serum testosterone remained suppressed at 313 days after the first dose despite recovery of menopausal gonadotropins by day 278 days. This illustrates use of multisteroid LCMS profiling for confirmation of the OHT diagnosis by ovarian and adrenal vein sampling and monitoring of treatment by peripheral blood sampling. Injection of a depot pure GnRH antagonist produced rapid and long-term complete suppression of ovarian steroidogenesis maintained over 10 months. Hence a depot

pure GnRH antagonist can not only rapidly confirm the OHT diagnosis but also induce long-term remission of severe hyperandrogenism without surgery.

Ovarian hyperthecosis (OHT) is a functional, nontumorous ovarian disorder characterized by excessive androgen secretion from an aberrant proliferation of hyperplastic luteinized theca calls within the ovarian stroma outside their usual location confined to the ovarian follicle wall. Intramural theca cells express luteinizing hormone (LH) receptors which are stimulated by circulating pituitary LH to synthesize androgens, including testosterone (T) and androgen precursors (DHEA, A_4). These androgens are transferred locally within the follicle to proximate granulosa cells which express aromatase to facilitate the enzymatic conversion of T, as an obligate precursor, to estradiol. In OHT, however, the hyperplastic luteinized theca cells ectopically located in the ovarian stroma [1] secrete excessive T and other androgen precursors into the circulation driven by high, menopausal circulating gonadotropins rather than remaining to be aromatized within the ovarian follicle. This is consistent with the strong preponderance of OHT with severe hyperandrogenism diagnosed after menopause. The present report describes the application of multisteroid liquid chromatography mass spectrometry (LCMS) profiling of selective ovarian and adrenal vein sampling with use of a long-acting depot gonadotropin-releasing hormone (GnRH) antagonist for rapid confirmation of diagnosis and long-term treatment of ovarian hyperandrogenism due to OHT.

Case Presentation

A 58-year-old female teacher presented with inadequately controlled steroid-induced type II diabetes. Investigations revealed a highly elevated (male range) serum T concentrations with virilization. She had frontal alopecia, hirsutism requiring depilation 2 or 3 times weekly, and progressive terminal hair growth on abdomen, back, and nipples. There was also mild acne on the face and back with unusual mood fluctuations over the preceding 18 months. There was no voice change, clitoral enlargement, or change in sexual activity. Her height was 165 cm, weight 64.2 kg (body mass index 23.6 kg/m^2). Her current medications included prednisolone (7 mg daily), tacrolimus (1 mg twice a day), mycophenolate (720 mg twice a day), calcitriol (0.5 mg twice a day), determir 34 units once daily in morning, and aspart 24 units 3 times a day.

She was born at 32 weeks' gestation from a twin pregnancy diagnosed during labor with failure to thrive during her first year. Chronic renal failure developed at age 17 years requiring dialysis and her first renal transplant which was rejected within months. After 3 years on dialysis, she underwent a second renal transplant that lasted for 31 years before failing. After a further 3 years of dialysis, she underwent a third renal transplant that had stable graft function (glomerular filtration rate 64 mL/min) when she presented 4 years later.

Menarche was at age 13 followed by regular menses and 2 easily conceived children with subsequent oral contraception till her husband's vasectomy. She had no history of polycystic ovary syndrome. Menopause at the age of 50 years passed without symptoms. She had metachronous ductal breast cancer in situ (3 years apart) with a positive family history treated with bilateral mastectomies but no chemo- or adjuvant hormonal therapy. She remained in remission 5 years after the second mastectomy. Other diagnoses included hyperparathyroidism and a submucosal uterine fibroid. She also had post-transfusion hepatitis C with secondary cirrhosis and portal hypertension. Following antiviral cure and around the same time as the finding of hyperandrogenism, regular hepatic ultrasound surveillance identified a 17.5-mm lesion hepatocellular carcinoma for which transarterial chemo-embolization with doxorubicin was undertaken. Follow-up imaging confirmed a complete radiologic response.

Serum T (Siemens Immulite immunoassay, RRID:AB_2756391) was 14 to 31.7 nmol/L (normal female <2 nmol/L) and confirmed in another laboratory by a different T immunoassay (22.5 nmol/L, Roche Elecsys, RRID:AB_2783736) and by LCMS (24.0 nmol/L) with serum androstenedione 40 nmol/L (LCMS, ref range 0.5-2.9 nmol/L). HbA1C was elevated (8.3-9.0%) with increased random blood glucose (6.6-18.1 mM). Biochemical, hematological, and hormonal profiles were unremarkable with menopausal serum LH (59-80 IU/L; Roche Cobas Elecsys LH, RRID:AB_2800498), follicle-stimulating hormone (FSH) (64-79 IU/L; Roche Cobas Elecsys FSH, RRID:AB_2800499), normal serum SHBG (52-96 nmol/L; Roche Elecsys SHBG, RRID:AB_2826621/2826678), glomerular filtration rate (54-66 mL/min), hemoglobin (134-142 g/L), and thyroid function (TSH 1.2-3.7 mIU/L, Roche Elecsys, RRID:AB_2801453; free thyroxine 15-16 pmol/L, Roche Elecsys, RRID:AB_2893401). No mass lesions were identified in the adrenal glands on computed

Table 1. Ovarian and adrenal vein sampling

Multisteroid profile	First venous sampling					Second venous sampling		
	Peripheral blood	Adrenal vein		Ovarian vein	Gradient ovary:periphery	Peripheral blood	Left ovarian vein	Gradient ovary:peripheral
		Right	Left	Left				
Progesterone (ng/mL)	0.1	nd	0.2	0.4	4.3	nd	0.5	/
17OHP$_4$ (ng/mL)	1.2	1.0	1.3	28.0	23.9	0.3	23.2	68.7
Estradiol (pg/mL)	25	14	15	129	5.2	50	86	1.7
Estrone (pg/mL)	104	66	68	223	2.1	70	263	3.8
A$_4$ (ng/mL)	8.0	5.8	5.5	157.0	19.6	2.2	146.0	66.4
T (ng/mL)	4.2	3.3	3.1	43.6	10.4	1.6	30.2	18.4
DHT (ng/mL)	0.39	0.26	0.48	0.53	1.4	0.17	0.14	0.8
DHEA (ng/mL)	2.38	1.42	1.67	35.0	14.7	0.32	24.6	76.2
3α androstanediol (ng/mL)	0.15	0.11	0.12	0.2	1.1	0.20	0.3	1.4
3β androstanediol (ng/mL)	0.05	nd	nd	nd	/	0.10	0.1	1.2
Cortisol (ng/mL)	12.1	11.2	63.1	9.8	0.8	6.5	11.2	1.7
17OHP$_5$ (ng/mL)	0.35	0.19	0.69	10.2	29.1	0.10	5.33	53.3
Pregnenolone (ng/mL)	nd	nd	0.25	1.66	/	nd	nd	/
Androsterone (ng/mL)	2.56	1.58	2.59	4.38	1.7	0.15	1.13	7.5
Androstenediol (ng/mL)	0.17	0.18	0.16	0.49	2.9	0.09	2.17	25.5

Steroid measurements by ultrapressure liquid chromatography mass spectrometry. To convert concentrations to SI units multiple by 3.18 (progesterone), 3.03 (17OHP$_4$), 3.66 (estradiol), 3.93 (estrone), 3.49 (A$_4$), 3.45 (T), 3.47 (DHT), 3.45 (DHEA), 3.42 (3α androstanediol), 3.42 (3β androstanediol), 2.76 (cortisol), 3.01 (17OHP$_5$), 3.16 (pregnenolone), 3.44 (androsterone), 3.42 (androstanediol).

Abbreviations: 17OHP$_4$, 17 hydroxyprogesterone; A$_4$, androstenedione; T, testosterone; DHT, dihydrotestosterone; DHEA, dehydroepiandrosterone; 17OHP$_5$, 17 hydroxypregnenolone; nd, not done.

tomography. Pelvic ultrasound demonstrated both ovaries of 4 mL volume but no mass lesions together with multiple uterine fibroids and an endometrial polyp.

Percutaneous catheterization of adrenal and ovarian veins via femoral vein was undertaken by experienced interventional radiologists. Serum concentrations of 15 steroids in venous samples (0.2 mL) were measured by a validated multisteroid ultrapressure LCMS method [2]. The left ovarian vein displayed strong gradients (10- to 30-fold) vs peripheral serum with gradients for serum 17 hydroxyprogesterone ($17OHP_4$), 17 hydroxypregnenolone ($17OHP_5$), androstenedione (A_4), and dehydroepiandrosterone (DHEA) all steeper than for serum T (Table 1). No adrenal vein gradients for T or other related sex steroids were observed. The right ovarian vein could not be cannulated. Four weeks later, immediately prior to the arterial transarterial chemo-embolization cannulation and at the same session, a second ovarian vein cannulation was repeated by the same radiologists. This cannulation confirmed strong left ovarian gradients (18-fold gradient T, >60-fold gradient 17OHP4, 17OHP5, A_4, DHEA) but right ovarian vein cannulation again could not be cannulated (Table 1).

The presumptive diagnosis was OHT with a wide range of ovarian steroid precursors and metabolites driven by high (menopausal) serum gonadotrophins. A single subcutaneous injection of a depot pure GnRH antagonist (80 mg Degarelix acetate, Ferring) produced a complete, rapid (within 24 hours) and sustained suppression of all ovarian steroids as well as serum LH and FSH lasting for at least 8 weeks (Table 2). Transient side-effects were injection site pain (redness, swelling, pain, lasting 2 days) and severe flushing, sweating, mood changes, and decreased concentration and fatigue in the second to third week post injection, alleviated by an estradiol patch but wearing off in the fourth week. Serum T remained undetectable with suppressed serum gonadotropins while virilization improved with reduction in hirsutism and acne. After a second degarelix injection at week 8, she again experienced immediate but transient injection site reaction and, between 2 and 5 weeks post injection, vaginal spotting with flushing, relieved by an estradiol patch. Her serum T remained undetectable despite gradual recovery of serum LH (9.8 IU/L) and FSH (17.0 IU/L). A pelvic ultrasound showed myometrial calcification within fibroids along with an echogenic vascular focus within the right ovary but no other space occupying lesions. Her facial features and hair growth continued to improve at more than 10 months after the first dose while her serum T remained undetectable but now accompanied by postmenopausal gonadotrophins (LH 52.1 U/L, FSH 60 U/L) by day 278 after first injection. After changes in her insulin regimen (glargine 34 units), her random blood glucose was 5.6 mM and HbA1c 6.3%.

Discussion

The differential diagnosis of hyperandrogenism in women depends on age and the level of serum T [3]. Among younger premenopausal women, mild hyperandrogenism (typically serum T <3 nmol/L) is mostly due to polycystic ovarian syndrome accounting for >70% of cases [4, 5]. Polycystic ovarian syndrome is the most frequent hormonal disorder of young women affecting between 6% and 12% [6-8] of reproductive age women with the mild hyperandrogenism persisting into older, postreproductive ages [9, 10] but is rarely responsible for severe hyperandrogenism with virilization.

Severe hyperandrogenism (serum T >7 nmol/L), well above normal female concentrations (<2 nmol/L) and into the eugonadal male range [11], is most frequently diagnosed in women after menopause [12]. Among postmenopausal women, severe hyperandrogenism may signify an underlying adrenal or ovarian tumor with high risk of malignancy thereby requiring diagnostic focus on steroidogenic tumors, initially by imaging. After menopause, androgen-secreting adrenal tumors are rare (1-2 cases per million per year [13]) and typically present as relatively large tumors facilitating diagnosis by computed tomography or magnetic resonance imaging. These imaging techniques must distinguish steroidogenically active tumors from incidental benign adrenal adenomas, which are relatively common (prevalence 5%) in otherwise healthy populations [14, 15], and may occur together by coincidence [16]. Androgen-secreting adrenal tumors typically secrete a spectrum of steroids with 25% also displaying cortisol hypersecretion [13] and 50% malignant [17, 18]. Ovarian androgen-secreting ovarian tumors are rarely malignant and often present with virilization arising from small tumors, often difficult to identify on imaging. Although in theory ovarian tumors are considered gonadotropin independent, some display partial gonadotropin dependence [19, 20]. OHT is the most frequent cause of nontumor-related severe hyperandrogenism (7/75, 9.3%). It is mostly diagnosed after menopause being rare among premenopausal women with 1 large series reporting no cases among 881 premenopausal women with hyperandrogenism [12], although rare cases are reported [20-22].

Retrograde venous cannulation to sample effluent blood from adrenal and ovarian veins to localize the organ secreting excessive steroids was first reported in 1971 [23]. This minimally invasive technique has been widely adopted to investigate cases of steroid-secreting tumors to lateralize and to distinguish them from nontumorous steroidogenic disorders. Such tests are typically required where imaging does not provide unequivocal tumor localization. Sampling venous effluent gradients provide complementary

Table 2. Effects of degarelix injections on multisteroid profile

Hormonal profile after degarelix injection

Time	17OHP$_4$ (ng/mL)	E2 (pg/mL)	E1 (pg/mL)	Adione (ng/mL)	T (ng/mL)	DHT (ng/mL)	DHEA (ng/mL)	17OHP$_5$ (ng/mL)	P$_5$ (ng/mL)	Androsterone (ng/mL)	Serum FSH (IU/L)	Serum LH (IU/L)	Serum SHBG (nM/L)
Day 0	1.54	37	122	8.12	4.72	0.40	2.15	0.60	0.06	3.30	67.1	73.2	57.6
+1 hour	1.49	37	112	7.87	4.60	0.32	1.61	0.55	0.11	3.75	71.1	73.8	64.9
+5.5 hour	1.51	46	130	7.78	4.65	0.33	2.68	0.34	0.07	2.32	60.0	44.9	61.4
Day 1	0.06	26	64	0.95	0.60	0.21	0.26	nd	nd	0.42	44.1	15.8	65.3
Day 2	nd	30	52	0.55	0.40	0.12	0.05	nd	nd	nd	33.4	8.9	59.5
Day 3	nd	26	28	0.22	0.11	0.12	0.09	nd	nd	nd	25.8	5.1	62.0
Day 4	nd	8	23	0.18	0.12	0.13	0.13	nd	nd	nd	19.9	3.1	58.4
Day 7	nd	16	18	0.08	0.03	0.16	nd	nd	nd	nd	10.9	1.2	58.9
Day 8	nd	18	13	0.04	nd	0.15	nd	nd	nd	nd	9.4	0.9	62.4
Day 9	nd	14	14	0.04	nd	0.16	0.05	nd	nd	nd	8.1	0.9	64.8
Day 10	0.06	25	11	0.08	nd	0.18	0.09	nd	nd	nd	6.5	0.6	63.0
Day 11	nd	13	16	0.03	nd	0.13	nd	nd	nd	nd	5.9	0.9	62.3
Day 18	0.06	79	23	0.04	nd	0.12	nd	nd	nd	nd	3.0	0.5	60.1
Day 25	0.07	101	57	0.04	nd	0.19	nd	0.07	nd	nd	12.0	4.2	73.3
Day 42	nd	nd	5	nd	nd	0.10	nd	0.10	nd	nd	9.0	3.3	84.90
Day 58 (2nd Injection)													
Day 74 (Inj2 + 17)					<0.3						5	1	
Day 88 (Inj2 + 31)					<0.3						4	0.4	
Day 111 (Inj2 + 54)											6	1.9	
Day 141 (Inj2 + 84)	nd	nd	7	0.04	nd	0.33	0.16	0.35	1.49	nd	8.5	7.2	90.2
Day 191 (Inj2 + 134)											17.0	9.8	
Day 278 (Inj2 + 221)					nd						60.0	52.1	
Day 313 (Inj2 + 256)	nd	14	8	nd	nd	nd	0.06	0.18	0.26	nd	71.4	81.3	71.4

Steroid concentrations by ultrapressure liquid chromatography (all samples except day 74, 88, 111, 191, and 278) and serum and peptides (serum LH, FSH, and SHBG) by immunoassay on days 74, 88, 111, 191, and 278.

For abbreviations and SI conversion factors see footnote to Table 1.

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; nd, nor detectable; SHBG, sex hormone binding globulin; T testosterone.

functional data and is more specific and diagnostic than dynamic stimulatory or suppressive tests. Yet anatomical variability makes venous cannulation of adrenal and ovarian veins technically challenging even for experienced interventional radiologists [24]. The left adrenal and ovarian veins drain into the left renal vein making it easier to locate their small exit points compared with the right adrenal and ovarian veins which drain directly into the vena cava but at an acute angle that may be too small, spasm prone or have exit valves. A series of 38 patients reported that successful sampling was more frequent for left vs right veins (80% vs 46%, respectively) and for adrenal vs ovarian veins (70% vs 57.5%, respectively) with the lowest success rate for right ovarian veins (42%) and only 27% of procedures successful sampling all 4 veins [25]. Comparable findings were reported in other series including 1 where, among 15 procedures, successful sampling of right ovarian vein (29%) was less frequent than left ovarian vein (64%) or either left (100%) or right (53%) adrenal veins [26]. Another series of 60 procedures confirmed the higher success rate for adrenal vs ovarian vein sampling (89% vs 69%) with the left ovarian vein (60%) most difficult to catheterize [27].

Measurement of steroid concentrations in venous effluent blood from cannulation studies have mostly relied on immunoassays. Immunoassays are designed to quantify a single analyte per assay, so a wide steroid profile requires large sample volume for multiple immunoassays, each specifically targeting a single steroid. Furthermore, the specificity of steroid immunoassays is limited by their crossreactivity with structurally related steroids such as precursors and metabolites. This creates difficulties for venous effluent samples from steroidogenic organs because the validation of specificity for steroid immunoassays is based on blood samples from healthy individuals. However, the spectrum of steroids in draining veins of steroidogenic organs differs markedly from circulating steroids necessitating rigorous additional validation for cross-reactivity when applying commercial steroid immunoassays to cannulation studies. These limitations are largely overcome in this study using a validated LCMS steroid profile measuring 15 related steroids in a single small (0.2 mL) sample, a volume readily obtained in venous cannulation studies. This steroid profile showed not only a steep gradient of ovarian to peripheral blood for serum T explaining the original presentation findings but even steeper gradients for several other steroid precursors ($17OHP_4$, $17OHP_5$, A_4, DHEA) than for T. As the unique clinical circumstances of this case allowed for an opportunistic second venous cannulation 4 weeks after the first, those second findings confirmed the consistency of gradients in steroid profiles. Analogous benefits of versatile multisteroid LCMS profiling of adrenal vein effluent for diagnosis of primary aldosteronism has recently been

reported [28] but we were unable to locate previous reports applied to ovarian vein sampling for hyperandrogenism.

The lack of a right adrenal to peripheral gradient was not unexpected due to the patient's prednisolone medication suppressing endogenous cortisol production. The cortisol gradient in the left adrenal vein may represent a coincidental burst of endogenous adrenal secretion. The consistently high ovarian vein DHEA concentration gradient with minimal right or left adrenal vein DHEA gradients indicates that in this case the ovary was the source of excess DHEA, contrary to the usual interpretation that DHEA is of exclusively adrenal origin.

The present wide steroid profile sheds light on previous reports of tumors reportedly secreting a single steroid [29]. The complexity of steroidogenesis [30] indicates that steroidogenically active tumors are likely to secrete multiple steroids, including precursors and metabolites of canonical bioactive steroids. The impression of selective secretion of only a single steroid may instead reflects the limitation of single analyte focus of steroid immunoassays as immunoassays inherently aim to be specific for a single analyte. For that purpose, steroidal profiling by mass spectrometry provides a wider appreciation of the spectrum of steroid secreted by pathological adrenal or ovarian disorders including tumor and nontumorous conditions.

Superactive GnRH analogs were first used for treatment of OHT in 1986 [31] and subsequently histrelin, buserelin, nafarelin, triptorelin, leuprolide, and goserelin have been widely used in depot formulations lasting 1 to 6 months [3, 16, 20-22, 32]. GnRH analogs were originally developed as superactive agonists aiming to produce sustained stimulation of GnRH secretion [33]. However, due to the physiological requirement for pulsatile release of GnRH to sustain pituitary gonadotropin secretion [34], superactive analogs produce a transient stimulatory phase ("flare") lasting up to 2 weeks before establishing desensitization of GnRH receptors leading to downregulation of pituitary gonadotropin and gonadal steroid secretion. Accordingly, use of superactive GnRH analogs in OHT features nonsuppression of ovarian steroidogenesis in the first 2 weeks after injection [31, 35, 36] but effective and sustained suppression of gonadotropins and ovarian steroidogenesis from 1 month onwards [16, 19-22, 32, 36-40]. Later pharmacological development of GnRH analogs produced pure GnRH antagonists [33, 41] such as ganirelix, degarelix, cetrorelix, and abarelix which featured immediate gonadotropin inhibition from onset of treatment eliminating the early transient "flare" phenomenon as well as later transient microsurges after each superactive agonist injection [42]. Accordingly, administration of a pure GnRH antagonist has been reported to rapidly (within 6-72 hours) suppress ovarian steroidogenesis

in postmenopausal women with severe hyperandrogenism [43-46], a finding we confirm and extend to multiple ovarian steroids. However, previous studies used short-term daily injections of the GnRH antagonists and the current standard of care suggests that such GnRH antagonist treatment is not a long-term treatment option [47]. The present case demonstrates the successful use of a depot pure GnRH antagonist to produce sustained resolution of ovarian hyperandrogenism in a case with a complex medical background making it desirable to avoid pelvic surgery. The consistent discrepancy between the speed of suppression of ovarian steroid and gonadotropin secretion, as well as the persistence of steroidogenic suppression when postmenopausal gonadotropin secretion resumed, suggests that the GnRH antagonist may have impact on ovarian as well as pituitary GnRH receptors [48, 49].

Nevertheless, as some ovarian tumors are difficult to visualize on imaging due to their small size and some are at least partially gonadotropin dependent [19, 20], the specificity of the rapid gonadotropin and steroidogenic response requires further evaluation. Hence the rapid, complete suppression of ovarian hyperandrogenism by a GnRH antagonist favors, but may not prove unequivocally, the diagnosis of OHT. Other depot GnRH antagonists would likely achieve the same result as may the newer, nonpeptide GnRH antagonists (elagolix, relugolix) if developed into depot formulations. Hence, the present case showing that a depot pure GnRH antagonist provides prolonged remission from ovarian hyperandrogenism due to OHT extends previous reports that a single dose of a pure GnRH antagonist provides rapid and effective confirmation of the diagnosis of OHT by adding new evidence that a depot pure GnRH antagonist can provide effective long-term treatment.

We conclude that in a postmenopausal woman with OHT, multisteroid profiling by LCMS of ovarian and adrenal vein samples together with an injection of a pure GnRH antagonist can provide rapid confirmation of diagnosis. Injection of a depot pure GnRH antagonist also provides highly effective, long-term treatment by remission of the aberrant ovarian steroidogenesis. When clinically desirable, these advantages of medical therapy may allow for deferral or avoidance of pelvic surgery to confirm a tissue diagnosis or perform an excision. Such pure GnRH antagonist treatment may have further clinical applications in severe ovarian hyperandrogenism.

Acknowledgments

Additional Information

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